

POPULATION PHARMACOKINETIC-PHARMACODYNAMIC ANALYSIS OF ZOLPIDEM TO EXPLORE SEX DIFFERENCES IN HEALTHY VOLUNTEERS



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OBJECTIVES

- Zolpidem is a non-benzodiazepine hypnotic agent used for the short-term treatment of insomnia, characterized by difficulty initiating sleep.
- According to the Food and Drug Administration (FDA) label for zolpidem, the recommended initial dose is 5 mg for adult women and 5 or 10 mg for adult men, reflecting the higher exposure observed in females compared to males.
- To better understand sex-related differences in the pharmacokinetics (PKs) and pharmacodynamics (PDs) of zolpidem, we comprehensively analyzed covariate effects in healthy male and female volunteers.

METHODS

- The population PK-PD model was sequentially developed using previously published data from 30 healthy volunteers (15 males and 15 females), including 325 data points for plasma zolpidem concentrations and 388 data points each for the digit symbol substitution test (DSST) score, choice reaction time (CRT), and sedation visual analog scale (VAS) score [1].
- Parameters were estimated using a nonlinear mixed-effects modeling approach with NONMEM (version 7.5.1) and first-order conditional estimation.
- Covariate effects were assessed using stepwise forward selection ($p < 0.05$) and backward elimination ($p < 0.01$).
- Candidate covariates included sex, age, weight, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, creatinine, and each baseline PD measure at 1h.

RESULTS

- The schematic structure of final population PK-PD model is shown in Figure 1.
- Goodness-of-fit plots and prediction-corrected visual predictive checks demonstrated that the model adequately described the observed zolpidem PK and PD profiles (Figure 2, Figure 3).

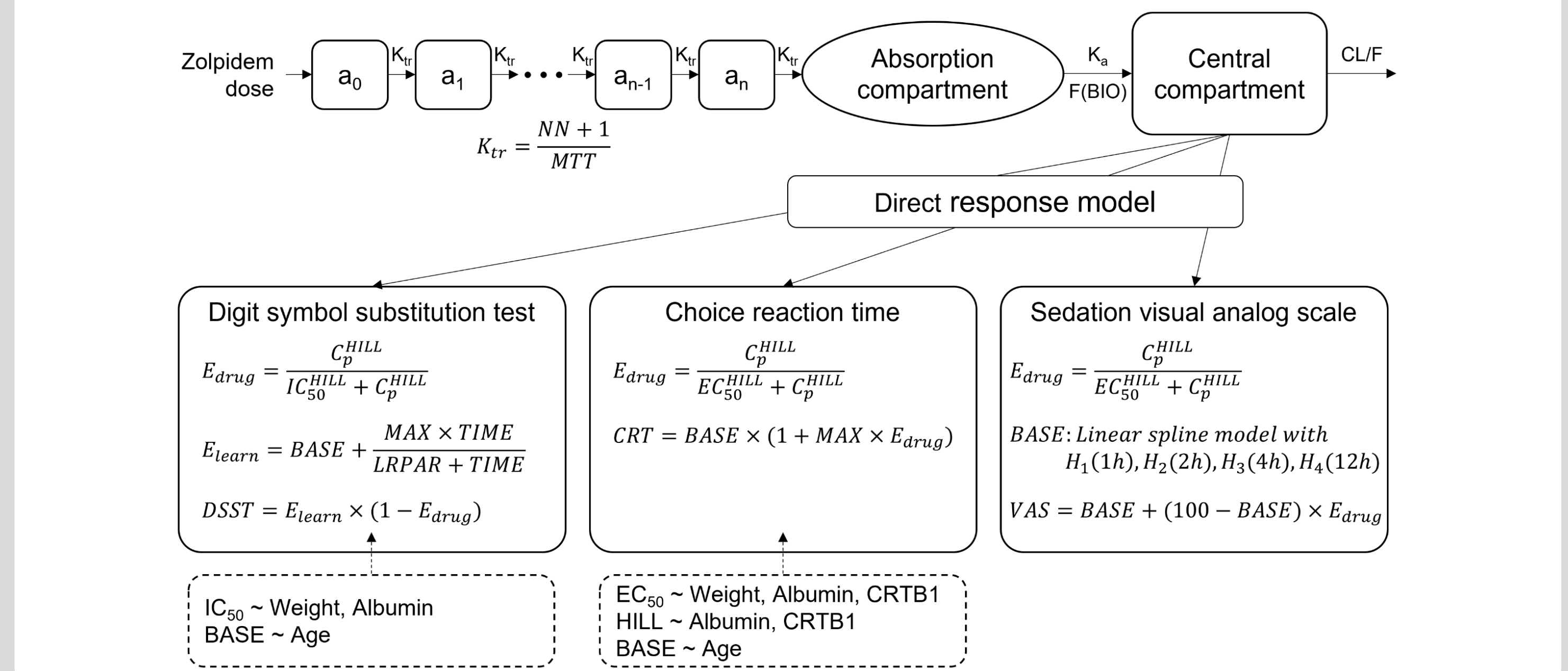


Figure 1. Final population pharmacokinetic-pharmacodynamic model structure for zolpidem.

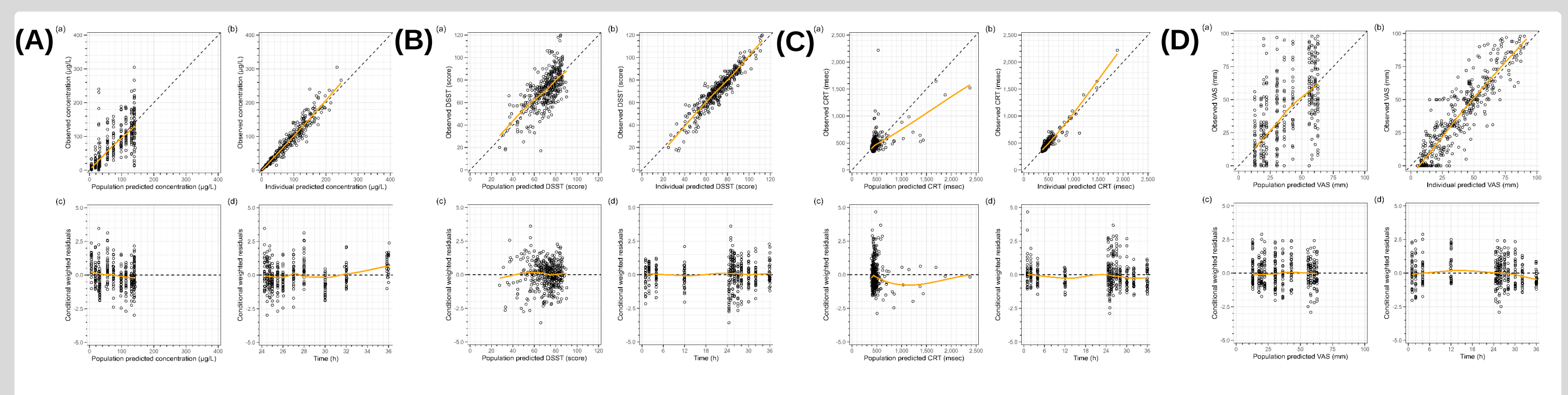


Figure 2. Goodness-of-fit plots of the final zolpidem population pharmacokinetic-pharmacodynamic model for (A) plasma zolpidem concentrations, (B) digit symbol substitution test, (C) choice reaction time, and (D) sedation visual analog scale.

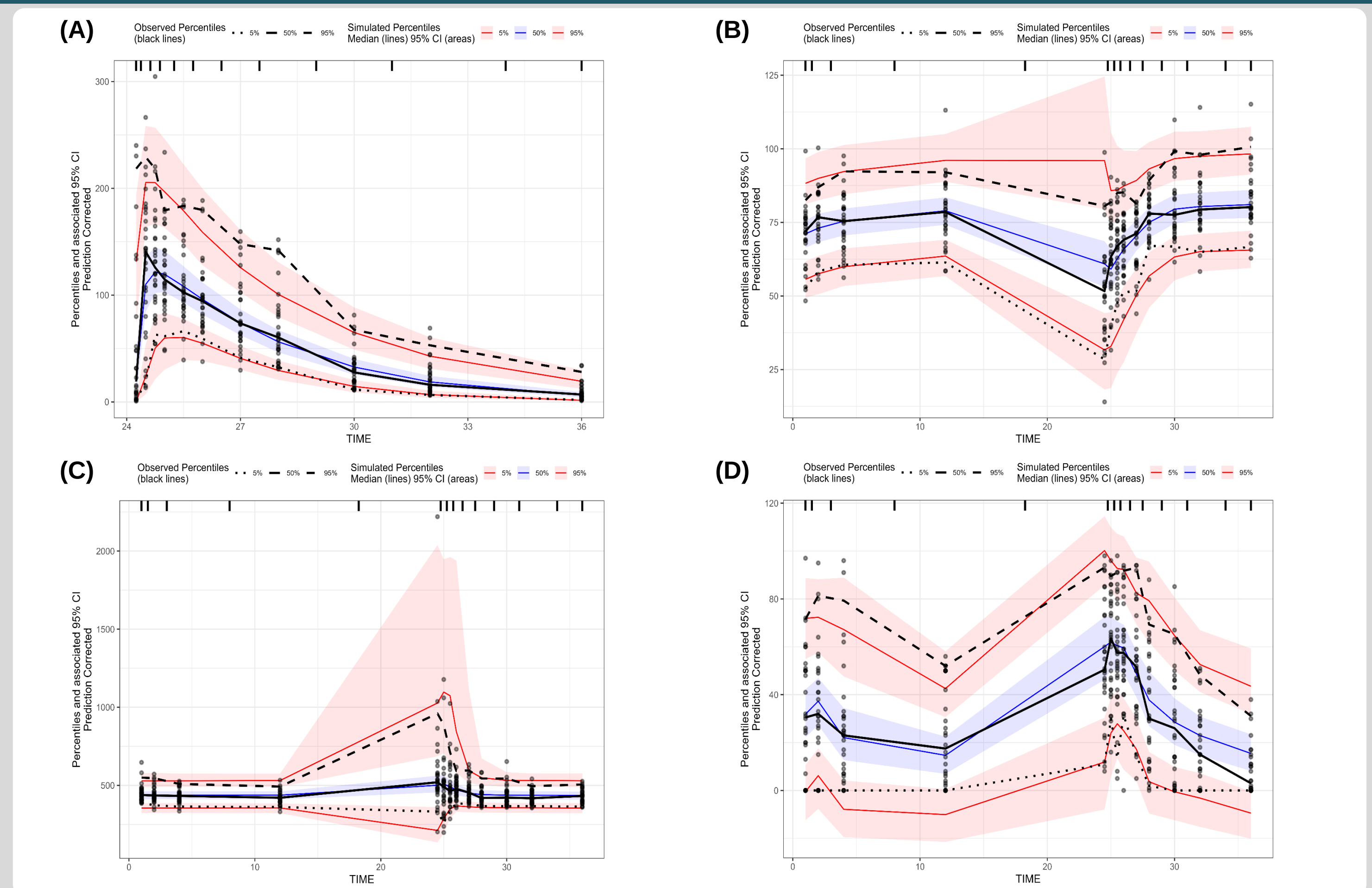


Figure 3. Prediction-corrected visual predictive checks of the final zolpidem population pharmacokinetic-pharmacodynamic model for (A) plasma zolpidem concentrations, (B) digit symbol substitution test, (C) choice reaction time, and (D) sedation visual analog scale.

Table 1. Population pharmacokinetic parameter estimates.

Pharmacokinetic parameter	Estimates (%RSE) [%Shrinkage]
K_a (h^{-1})	11.7 (36.8)
MTT (h)	0.25 (8.4)
NN	19.4 (18.8)
CL/F (L/h)	18.0 (7.9)
V_d/F (L)	64.0 (4.9)
BIO	1 Fixed
IIV K_a (%CV)	330.8 (30.7) [27.9]
IIV MTT (%CV)	37.7 (51.0) [20.0]
IIV CL/F (%CV)	24.1 (28.1) [4.70]
IIV BIO (%CV)	25.9 (25.3) [5.50]
Proportional residual error (%)	18.9 (7.20)

Notes: The percentage of coefficient of variation (%CV) was calculated as $100 \times \sqrt{\exp(\omega^2) - 1}$.

Abbreviations: BIO, bioavailability; CL, confidence interval; CL/F, apparent clearance; CV, coefficient of variation; IIV, inter-individual variability; K_a , absorption rate constant; MTT, mean transit time; NN, number of transit compartments; RSE, relative standard error; V_d/F , apparent central volume of distribution.

Table 2. Population pharmacodynamic parameter estimates.

Pharmacodynamic parameter	Estimates (%RSE) [%Shrinkage]	Pharmacodynamic parameter	Estimates (%RSE) [%Shrinkage]	Pharmacodynamic parameter	Estimates (%RSE) [%Shrinkage]
Digit symbol substitution test		Choice reaction time		Sedation visual analog scale	
IC_{50} ($\mu g/L$) ^a	205 (7.5)	EC_{50} ($\mu g/L$) ^c	282 (8.5)	EC_{50} ($\mu g/L$)	146 (12.7)
Effect of weight	-1.57 (24.3)	Effect of weight	-0.0193 (14.1)	HILL	1.92 (16.3)
Effect of albumin	0.541 (41.6)	Effect of albumin	3.89 (29.8)	H_1 (mm/100)	0.303 (17)
HILL	2.54 (11.1)	Effect of CRTB1	-1.28 (26.1)	H_2 (mm/100)	0.362 (13.5)
BASE (score) ^b	68.2 (3.3)	HILL ^d	6 (8.8)	H_3 (mm/100)	0.198 (26.6)
Effect of age	-0.0143 (23.1)	Effect of albumin	-5.26 (21.7)	H_4 (mm/100)	0.127 (20.9)
MAX (score)	14.4 (10.6)	Effect of CRTB1	0.00637 (15.7)		
LRPAR (h)	4.3 (38.6)	BASE (msec) ^e	437 (1.8)		
		Effect of age	0.0112 (22.2)	IIV EC_{50} (%CV)	53.9 (44.7) [20]
		MAX	5.6 Fixed	IIV H_1 ^f	1.03 (44.6) [20.6]
IIV IC_{50} (%CV)	22.3 (28.9) [15.2]	IIV EC_{50} (%CV)	21.1 (35.1) [20.2]	IIV H_2 ^f	0.653 (49.0) [22.1]
IIV BASE (%CV)	13.1 (28.9) [3]	IIV BASE (%CV)	9.4 (27.6) [4.4]	IIV H_3 ^f	1.7 (37.9) [19.9]
		IIV HILL (%CV)	-	IIV H_4 ^f	0.699 (40.9) [30.6]
Additive residual error (score)	6 (5.8)	Proportional residual error (%)	9.42 (7.2)	Additive residual error (mm)	14.4 (5.5)

Notes: The percentage of coefficient of variation (%CV) was calculated as $100 \times \sqrt{\exp(\omega^2) - 1}$.

^a $IC_{50,DSST}$ ($\mu g/L$) = $205 \times (\text{Weight}/60.05)^{-1.57} \times (1 + 0.541 \times (\text{Albumin} - 4.4))$

^b $BASE_{DSST}$ (score) = $68.2 \times (1 - 0.0143 \times (\text{Age} - 29.5))$

^c $EC_{50,CRT}$ ($\mu g/L$) = $282 \times (1 - 0.0193 \times (\text{Weight} - 60.05)) \times (\text{Albumin}/4.4)^{3.89} \times (\text{CRTB1}/438.5)^{-1.28}$

^d $HILL_{CRT}$ = $6 \times (\text{Albumin}/4.4)^{-5.26} \times (1 + 0.00637 \times (\text{CRTB1} - 438.5))$

^e $BASE_{CRT}$ (msec) = $437 \times (1 + 0.0112 \times (\text{Age} - 29.5))$

^fThe IIV was modeled as an additive effect on the logit-transformed baseline VAS (Day -1) and expressed as ω^2 instead of %CV.

Abbreviations: BASE, the baseline pharmacodynamic measurement; CRT, choice reaction time; CRTB1, the baseline CRT value at 1 hour on Day -1; CV, coefficient of variation; DSST, digit symbol substitution test; EC_{50} , the half-maximal effective concentration of zolpidem in plasma; H_1 , VAS measurement at 1 hour on Day -1; H_2 , VAS measurement at 2 hours on Day -1; H_3 , VAS measurement at 4 hours on Day -1; H_4 , VAS measurement at 12 hours on Day -1; HILL, Hill coefficient; IC_{50} , the half-maximal inhibitory concentration of zolpidem in plasma; IIV, inter-individual variability; LRPAR, the time to half-maximal learning effect; MAX, the maximum drug effect parameter, expressed as either an additive change (DSST) or a proportional change (CRT) from baseline; VAS, sedation visual analog scale.

- The medians of the parameters obtained from 1000 bootstrap replicates were comparable to the parameter estimates in the final models.
- In the forest plot, weight at the 90th percentile (78.0 kg) was associated with a clinically relevant reduction in $IC_{50,DSST}$ and $EC_{50,CRT}$ relative to 60.05 kg, with point estimates [90% CI] of 0.66 [0.60–0.77] and 0.65 [0.59–0.77], respectively (Figure 4).

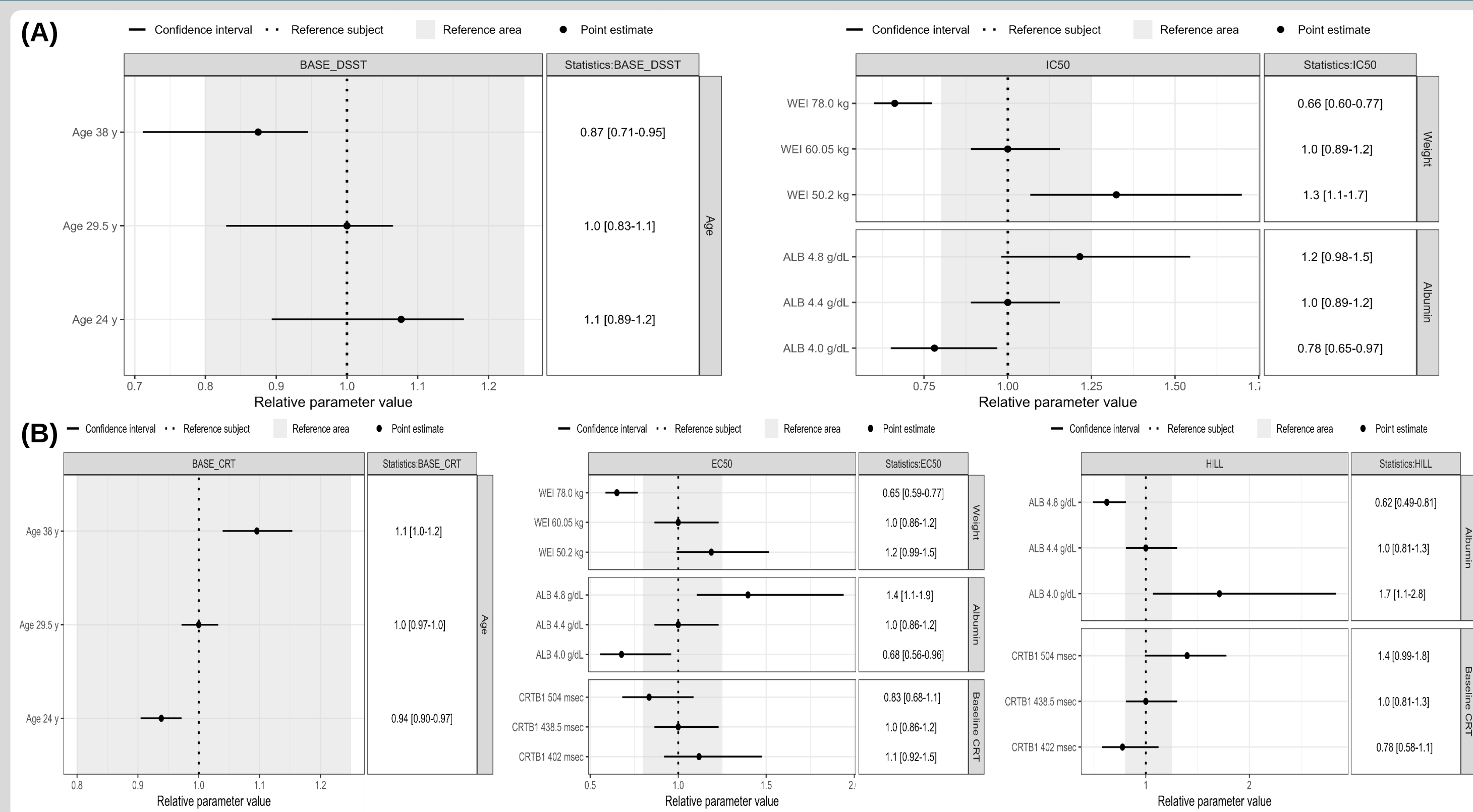


Figure 4. Forest plots illustrating the effects of covariates on (A) the baseline DSST values and IC_{50} and (B) the baseline CRT values, EC_{50} , and HILL based on the final zolpidem population pharmacokinetic-pharmacodynamic model.

CONCLUSION

- Zolpidem exhibited increased potency with higher weight and lower albumin, while older age was associated with lower baseline DSST scores and higher baseline CRT times, leading to reduced response.
- Since weight and albumin differ significantly between males and females in the dataset, these covariates might contribute to observed differences between sexes.
- The proposed population PK-PD models suggest that weight, albumin, age, and baseline PD measures, rather than sex, are the primary determinants of zolpidem's pharmacodynamic response.

REFERENCES

- [1] Yoon, S., Jeong, S., Jung, E. *et al.* Effect of CYP3A4 metabolism on sex differences in the pharmacokinetics and pharmacodynamics of zolpidem. *Sci Rep* 11, 19150 (2021). <https://doi.org/10.1038/s41598-021-98689-z>
- [2] Trocóniz, I.F., Boland, K. & Staab, A. Population Pharmacokinetic/Pharmacodynamic Model for the Sedative Effects of Flibanserine in Healthy Volunteers. *Pharm Res* 29, 1518–1529 (2012). <https://doi.org/10.1007/s11095-011-0648-6>